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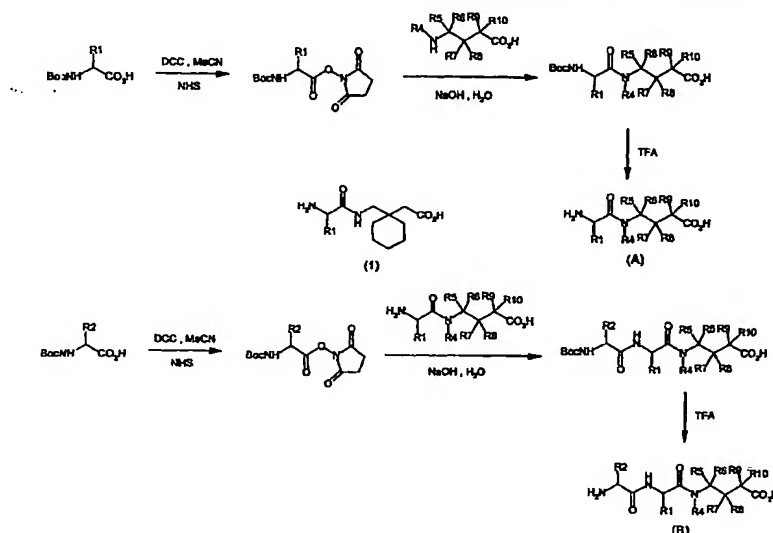
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(54) Title: AMINO ACID CONJUGATES PROVIDING FOR SUSTAINED SYSTEMIC CONCENTRATIONS OF GABA ANALOGUES

Synthesis of Aminoacyl and Other Peptide Derivatives of GABA Analogs



(57) Abstract: This invention is directed to compounds that provide for sustained systemic concentrations of GABA analogs following administration to animals. This invention is also directed to pharmaceutical compositions including and methods using such compounds.



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5 **AMINO ACID CONJUGATES PROVIDING FOR SUSTAINED
 SYSTEMIC CONCENTRATIONS OF GABA ANALOGUES**

10 **BACKGROUND OF THE INVENTION**

15 Field of the Invention

 This invention is directed to compounds that provide for sustained
 systemic concentrations of GABA analogs following administration to animals.
 This invention is also directed to pharmaceutical compositions including and
15 methods using such compounds.

State of the Art

 Rapid clearance of drugs from the systemic circulation represents a major
 impediment to effective clinical use of therapeutic and/or prophylactic
20 compounds. Although multiple factors can influence the systemic concentrations
 of drugs achieved following administration (including drug solubility, dissolution
 rate, first-pass metabolism, p-glycoprotein and related efflux mechanisms,
 hepatic/renal elimination, etc), rapid systemic clearance is a particularly
 significant reason for suboptimal systemic exposure to many compounds. Rapid
25 systemic clearance may require that large doses of drug be administered to
 achieve a therapeutic or prophylactic effect. Such larger doses of the drug,
 however, may result in greater variability in drug exposure, more frequent
 occurrence of side effects, or decrease in patient compliance. Frequent drug
 administration may also be required to maintain systemic drug levels above a
30 minimum effective concentration. This problem is particularly significant for
 drugs that must be maintained in a well-defined concentration window to provide
 continuous therapeutic or prophylactic benefit while minimizing adverse effects
 (including for example, antibacterial agents, antiviral agents, anticancer agents,
 anticonvulsants, anticoagulants, etc.).

35

Conventional approaches to extend the systemic exposure of drugs with rapid clearance involve the use of formulation or device approaches that provide a slow or sustained release of drug within the intestinal lumen. These approaches are well known in the art and normally require that the drug be well absorbed from the large intestine, where such formulations are most likely to reside while releasing the drug. Drugs that are amenable to conventional sustained release approaches must be orally absorbed in the intestine and traverse this epithelial barrier by passive diffusion across the apical and basolateral membranes of the intestinal epithelial cells. The physicochemical features of a molecule that favor its passive uptake from the intestinal lumen into the systemic circulation include low molecular weight (e.g. < 500 Da), adequate solubility, and a balance of hydrophobic and hydrophilic character (logP generally 1.5-4.0) (Navia and Chaturvedi, P. R. *Drug Discovery Today* 1996, 1, 179-189).

Polar or hydrophilic compounds are typically poorly absorbed through an animal's intestine as there is a substantial energetic penalty for passage of such compounds across the lipid bilayers that constitute cellular membranes. Many nutrients that result from the digestion of ingested foodstuffs in animals, such as amino acids, di- and tripeptides, monosaccharides, nucleosides and water-soluble vitamins, are polar compounds whose uptake is essential to the viability of the animal. For these substances there exist specific mechanisms for active transport of the solute molecules across the apical membrane of the intestinal epithelia. This transport is frequently energized by co-transport of ions down a concentration gradient. Solute transporter proteins are generally single sub-unit, multi-transmembrane spanning polypeptides, and upon binding of their substrates are believed to undergo conformational changes, which result in movement of the substrate(s) across the membrane.

Over the past 10-15 years, it has been found that a number of orally administered drugs are recognized as substrates by some of these transporter proteins, and that this active transport may largely account for the oral absorption

of these molecules (Tsuji and Tamai, *Pharm. Res.* 1996, 13, 963-977). While in most instances the transporter substrate properties of these drugs were unanticipated discoveries made through retrospective analysis, it has been appreciated that, in principle, one might achieve good intestinal permeability for a drug by designing in recognition and uptake by a nutrient transport system. Drugs subject to active absorption in the small intestine are often unable to passively diffuse across epithelial cell membranes and are too large to pass through the tight junctions that exist between the intestinal cells. These drugs include many compounds structurally related to amino acids, dipeptides, sugars, nucleosides, etc. (for example, many cephalosporins, ACE inhibitors, AZT, gabapentin, pregabalin, baclofen, etc.)

One pathway that might provide for the sustained delivery of drugs with rapid systemic clearance is the proton-coupled peptide transporters (Leibach and Ganapathy, *Ann. Rev. Nutr.* 1996, 16, 99-119). Such transporters mediate the cellular uptake of small intact peptides consisting of two or three amino acids and are found primarily in the intestine and kidney. In the intestine, where small peptides are not well-absorbed through passive diffusion, the transporters act as a vehicle for their effective absorption. Transporters in the kidney actively reabsorb di- and tri-peptides from the glomerular filtrate, thereby increasing their half-life in the circulation.

Two proton-coupled peptide transporters that have been cloned and characterized are PEPT1 and PEPT2. PEPT1 is a low-affinity, high-capacity transporter found primarily in the intestine. The human PEPT1 consists of 708 amino acids and possesses 12 putative transmembrane domains. PEPT2, in contrast, is a high-affinity, low-capacity transporter found mostly in the kidney. It consists of 729 amino acids and is 50% identical to human intestinal PEPT1.

Studies of PEPT1 and PEPT2 have shown that the transporters account for the absorption and reabsorption of certain therapeutically active compounds. The compounds include both biologically active peptides (e.g., renin inhibitors) and

zwitterionic antibiotics. Based on these observations, researchers have suggested that peptide transporters, in conjunction with cytosolic peptidases, could be exploited for systemic delivery of certain drugs in the form of peptide prodrugs. Dipeptide analogues of α -methyldopa, L- α -methyldopa-Phe and L- α -methyldopa-Pro, for example, are absorbed more efficiently in the intestine than α -methyldopa alone. Once across the intestinal membrane, the dipeptides are hydrolyzed by cytosolic peptidases to release α -methyldopa.

While the general suggestion of exploiting proton-coupled peptide transporters to enhance the absorption of poorly absorbed drugs has been made, the existing art does not teach a method that can be used successfully to design and construct a peptide prodrug of any given drug. Moreover, the existing art merely discusses improving intestinal absorption of poorly absorbed drugs. It does not teach the exploitation of PEPT1 or PEPT2 to achieve sustained systemic concentrations of drugs following administration to animals.

SUMMARY OF THE INVENTION

This invention is directed to the surprising discovery that PEPT1 and PEPT2 oligopeptide transporters can be utilized to provide sustained systemic concentrations of drugs administered to an animal. This invention, therefore, permits sustained therapeutic or prophylactic systemic blood concentrations of GABA analogues which heretofore could not be achieved.

Accordingly, in one of its compound aspects, this invention is directed to a compound of formula (I):



wherein

I is $-\text{NR}^{50}-(\text{CR}^{51}\text{R}^{52})_a-(\text{CR}^{53}\text{R}^{54})_b-\text{C}(\text{O})-$;

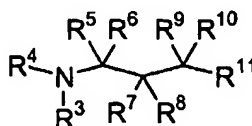
J is $-\text{NR}^{55}-(\text{CR}^{56}\text{R}^{57})_c-(\text{CR}^{58}\text{R}^{59})_d-\text{C}(\text{O})-$;

K is $-\text{NR}^{60}-(\text{CR}^{61}\text{R}^{62})_e-(\text{CR}^{63}\text{R}^{64})_f\text{C}(\text{O})-$;

wherein a, b, c, d, e and f are independently 0 or 1, provided that at least one of a and b is 1, at least one of c and d is 1, and at least one of e and f is 1;

and wherein i, j and k are independently 0 or 1, provided that at least one of i, j and k is 1;

D is a moiety derived from a GABA analog having the following structure:



wherein

R^3 is a covalent bond linking the GABA analog moiety to J_j ;

R^4 is hydrogen, or R^4 and R^9 together with the atoms to which they are attached form a heterocyclic ring;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, or R^7 and R^8 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{11} is $\text{C}(\text{O})\text{R}^{12}$, wherein R^{12} is a covalent bond linking the GABA analog moiety to K_k ;

R^{50} is hydrogen or R^{50} and R^{51} together with the atoms to which they are attached form a heterocyclic ring;

R⁵¹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁵¹ and R⁵² together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R⁵¹ and R⁵³ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁵² is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁵³ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁵³ and R⁵⁴ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁵⁴ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁵⁵ is hydrogen or R⁵⁵ and R⁵⁶, together with the atoms to which they are attached form a heterocyclyl ring;

R⁵⁶ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁵⁶ and R⁵⁷ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R⁵⁶ and R⁵⁸ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁵⁷ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁵⁸ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl,

substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁵⁸ and R⁵⁹ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁵⁹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁶⁰ is hydrogen or R⁶⁰ and R⁶¹, together with the atoms to which they are attached form a heterocyclyl ring;

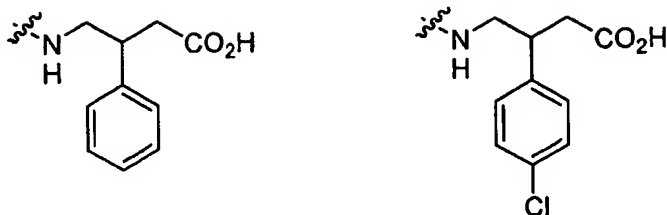
R⁶¹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁶¹ and R⁶² together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R⁶¹ and R⁶³ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁶² is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁶³ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁶³ and R⁶⁴ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁶⁴ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

and provided that when D is either of the following moieties



neither I or J are selected from a group of moieties selected from the following moieties: H₂NCH₂C(O)-, H₂NCH(CH₃)C(O)-, NH₂CH₂CH₂C(O)- and

5

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the synthesis of aminoacyl and other peptide derivatives of GABA analogs.

10

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to compounds that provide for sustained systemic concentrations of GABA analogues or active metabolites thereof following administration to animals. This invention is also directed to methods using the compounds and pharmaceutical compositions that are used in such methods. However, prior to describing this invention in further detail, the following terms will first be defined:

15

Definitions

20

As used herein, the term "animal" refers to various species such as mammalian and avian species including, by way of example, humans, cattle, sheep, horses, dogs, cats, turkeys, chicken, and the like. Preferably, the animal is a mammal and even more preferably is a human.

25

"Administering to the animal" refers to delivering a compound of formula (I) to an animal through a suitable route. Such routes include, for example, oral,

rectal, subcutaneous, intravenous, intramuscular and intranasal. Preferably, the compound is orally administered to the animal.

5 “Orally delivered drugs” refer to drugs which are administered to an animal in an oral form, preferably, in a pharmaceutically acceptable diluent. Oral delivery includes ingestion of the drug as well as oral gavage of the drug.

10 “PEPT1 oligopeptide transporter” refers to a type of protein that absorbs peptides in certain tissues, such as the intestine. This transporter is described and characterized in the literature. See Adibi, S. A., *Gastroenterology* 1997, 113, 332-340 and Leibach *et al.*, *Ann. Rev. Nutr.* 1996, 16, 99-119 for a discussion of the transporter.

15 “PEPT2 oligopeptide transporter” refers to a type of protein that absorbs peptides in certain tissues, such as the kidney. This transporter is described and characterized in the literature. See Dieck, S. T. *et al.*, *GLIA* 1999, 25, 10-20, Leibach *et al.*, *Ann. Rev. Nutr.* 1996, 16, 99-119; and Wong *et al.*, *Am. J. Physiol.* 1998, 275, C967-C975 for a discussion of the transporter.

20 “Transported by either a PEPT1 or PEPT2 oligopeptide transporter” refers to the translocation of a molecule across a membrane of a cell expressing the transporter. The translocation occurs through interaction with the transporter and is energized by cotransport of H⁺ ions across the membrane.

25 “Amino acid” is intended to denote α -amino acids and β -amino acids only. α -Amino acids are molecules of the formula:



wherein:

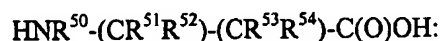
30 R⁵⁰ is hydrogen or R⁵⁰ and R⁵¹ together with the atoms to which they are attached form a heterocyclyl ring;

R^{51} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{51} and R^{52} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R^{52} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl.

β -Amino acids are molecules of formula:

10



wherein:

R^{50} is hydrogen or R^{50} and R^{51} together with the atoms to which they are attached form a heterocyclyl ring;

15

R^{51} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{51} and R^{52} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R^{51} and R^{53} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

20

R^{52} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

25

R^{53} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{53} and R^{54} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

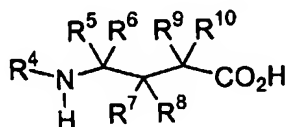
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R^{54} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl.

“Naturally occurring amino acid” refers to any of the alpha-amino acids that are the chief components of proteins. The amino acids are either synthesized by living cells or are obtained as essential components of the diet. Such amino acids include, for example, the following: alanine, arginine, asparagines, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

“Derived from a compound” refers to a moiety that is structurally related to such a compound. The structure of the moiety is identical to the compound except at 1 or 2 positions. At these positions, either a hydrogen atom attached to a heteroatom or a hydroxyl moiety of a carboxylic acid group has been replaced with a covalent bond that serves as a point of attachment to another moiety. For example, the moiety $\text{-NHCH}_2\text{C(O)-}$ is derived from glycine. In the moiety, both a hydrogen atom on the amino group and a hydroxyl portion of the carboxyl group have been replaced with a covalent bond.

“GABA analog” refers to a compound of the following structure:



wherein

R^4 is hydrogen, or R^4 and R^9 together with the atoms to which they are attached form a heterocyclic ring;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R⁷ and R⁸ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, or R⁷ and R⁸ together with the atoms to which they are attached form a cycloalkyl substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

R⁹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl; and,

R¹⁰ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

“Systemic bioavailability” refers to the rate and extent of systemic exposure to a drug or a metabolite thereof as reflected by the area under the systemic blood concentration versus time curve.

“Translocation across the intestinal wall” refers to movement of a drug or drug conjugate by a passive or active mechanism, or both, across an epithelial cell membrane of any region of the gastrointestinal tract.

“Active metabolite of a drug” refers to products of *in vivo* modification of the drug which have therapeutic or prophylactic effect.

“Therapeutic or prophylactic blood concentrations” refers to systemic exposure to a sufficient concentration of a drug or an active metabolite thereof over a sufficient period of time to effect disease therapy or to prevent the onset or reduce the severity of a disease in the treated animal.

“Sustained release” refers to release of a drug or an active metabolite thereof into the systemic circulation over a prolonged period of time relative to that achieved by oral administration of a conventional formulation of the drug.

“Tissue of the enterohepatic circulation” refers to the blood, plasma, intestinal contents, intestinal cells, liver cells, biliary tract or any fraction, suspension, homogenate, extract or preparation thereof.

5 “Conjugating” refers to the formation of a covalent bond.

 “Active transport or active transport mechanism” refers to the movement of molecules across cellular membranes that: a) is directly or indirectly dependent on an energy mediated process (i.e. driven by ATP hydrolysis, ion gradient, etc);
10 or b) occurs by facilitated diffusion mediated by interaction with specific transporter proteins; or c) occurs through a modulated solute channel.

 “Amino-protecting group” or “amino-blocking group” refers to any group which when bound to one or more amino groups prevents reactions from
15 occurring at these amino groups and which protecting groups can be removed by conventional chemical steps to reestablish the amino group. The particular removable blocking group is not critical and preferred amino blocking groups include, by way of example only, t-butyloxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), and the like.

20 “Carboxyl-protecting group” or “carboxyl-blocking group” refers to any group which when bound to one or more carboxyl groups prevents reactions from occurring at these groups and which protecting groups can be removed by conventional chemical steps to reestablish the carboxyl group. The particular
25 removable blocking group is not critical and preferred carboxyl blocking groups include, by way of example only, esters of the formula –COOR” where R” is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, alkaryl, substituted alkaryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted
30 heterocyclic.

"Amino acid sidechains" refer to the sidechains of naturally occurring amino acids which are well known in the art.

"Alkyl" refers to alkyl groups preferably having from 1 to 20 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, *t*-butyl, *n*-heptyl, octyl, dodecyl and the like.

"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 20 carbon atoms, having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxylaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl,

-NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

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"Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

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"Substituted alkoxy" refers to the group "substituted alkyl-O-".

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O), heterocyclic-C(O)-, and substituted heterocyclic-C(O)- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

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"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl,

substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thiocarbonylamino" refers to the group -C(S)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Alkenyl" refers to alkenyl group preferably having from 2 to 20 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocabonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted

alkenyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

"Alkenyloxy" refers to the group -O-alkenyl.

"Substituted alkenyloxy" refers to the group -O-substituted alkenyloxy.

"Alkynyl" refers to alkynyl group preferably having from 2 to 20 carbon atoms and more preferably 3 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation.

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"Substituted alkynyl" refers to alkynyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl,

-OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl,
 -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is
 hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl,
 -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,
 5 -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl,
 -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted
 aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl,
 -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is
 hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted
 10 alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino,
 mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino,
 mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino,
 unsymmetric di-substituted amines having different substituents selected from the
 group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl,
 15 substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted
 alkynyl groups having amino groups blocked by conventional blocking groups
 such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups
 substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted
 alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted
 20 aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic,
 -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

"Alkylene" refers to a divalent alkylene group preferably having from 1 to
 20 carbon atoms and more preferably 1 to 6 carbon atoms. This term is
 25 exemplified by groups such as methylene (-CH₂-), ethylene (-CH₂CH₂-), the
 propylene isomers (e.g., -CH₂CH₂CH₂- and -CH(CH₃)CH₂-) and the like.

"Substituted alkylene" refers to alkylene groups having from 1 to 5
 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl,
 30 acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino,
 thioamidino, aminoacyl, aminocarbonylamino, aminothiocabonylamino,
 aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy,

aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl,
 carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl,
 carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,
 carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic,
 5 carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino,
 guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted
 thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted
 thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl,
 substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy,
 10 substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy,
 heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino,
 oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl,
 -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl,
 -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is
 15 hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl,
 -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,
 -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl,
 -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted
 aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl,
 20 -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is
 hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted
 alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino,
 mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino,
 mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino,
 25 unsymmetric di-substituted amines having different substituents selected from the
 group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl,
 substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted
 alkenyl groups having amino groups blocked by conventional blocking groups
 such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups
 30 substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted
 alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted
 aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic,

-SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

"Alkenylene" refers to a divalent alkenylene group preferably having from 2 to 20 carbon atoms and more preferably 1 to 6 carbon atoms and having from 1 to 2 sites of alkenyl unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), propenylene (-CH₂CH=CH-), and the like.

"Substituted alkenylene" refers to alkenylene groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocabonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl,

-NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted alkenyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

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"Alkynylene" refers to a divalent alkynylene group preferably having from 2 to 20 carbon atoms and more preferably 1 to 6 carbon atoms and having from 1 to 2 sites of alkynyl unsaturation. This term is exemplified by groups such as ethynylene, propynylene and the like.

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"Substituted alkynylene" refers to alkynylene groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted

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thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and substituted alkenyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

"Amidino" refers to the group H₂NC(=NH)- and the term "alkylamidino" refers to compounds having 1 to 3 alkyl groups (e.g., alkylHNC(=NH)-).

"Thioamidino" refers to the group RSC(=NH)- where R is hydrogen or alkyl.

"Aminoacyl" refers to the groups -NRC(O)alkyl , $\text{-NRC(O)substituted alkyl}$, -NRC(O)cycloalkyl , $\text{-NRC(O)substituted cycloalkyl}$, -NRC(O)alkenyl , $\text{-NRC(O)substituted alkenyl}$, -NRC(O)alkynyl , $\text{-NRC(O)substituted alkynyl}$, -NRC(O)aryl , $\text{-NRC(O)substituted aryl}$, -NRC(O)heteroaryl , $\text{-NRC(O)substituted heteroaryl}$, $\text{-NRC(O)heterocyclic}$, and $\text{-NRC(O)substituted heterocyclic}$ where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonyloxy" refers to the groups -NRC(O)O-alkyl , $\text{-NRC(O)O-substituted alkyl}$, -NRC(O)O-alkenyl , $\text{-NRC(O)O-substituted alkenyl}$, -NRC(O)O-alkynyl , $\text{-NRC(O)O-substituted alkynyl}$, $\text{-NRC(O)O-cycloalkyl}$, $\text{-NRC(O)O-substituted cycloalkyl}$, -NRC(O)O-aryl , $\text{-NRC(O)O-substituted aryl}$, $\text{-NRC(O)O-heteroaryl}$, $\text{-NRC(O)O-substituted heteroaryl}$, $\text{-NRC(O)O-heterocyclic}$, and $\text{-NRC(O)O-substituted heterocyclic}$ where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Oxycarbonylamino" refers to the groups -OC(O)NH_2 , -OC(O)NRR , -OC(O)NR-alkyl , $\text{-OC(O)NR-substituted alkyl}$, -OC(O)NR-alkenyl , $\text{-OC(O)NR-substituted alkenyl}$, -OC(O)NR-alkynyl , $\text{-OC(O)NR-substituted alkynyl}$, $\text{-OC(O)NR-cycloalkyl}$, $\text{-OC(O)NR-substituted cycloalkyl}$, -OC(O)NR-aryl , $\text{-OC(O)NR-substituted aryl}$, $\text{-OC(O)NR-heteroaryl}$, $\text{-OC(O)NR-substituted heteroaryl}$, $\text{-OC(O)NR-heterocyclic}$, and $\text{-OC(O)NR-substituted heterocyclic}$ where R is hydrogen, alkyl or where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted

heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

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"Oxythiocarbonylamino" refers to the groups -OC(S)NH₂, -OC(S)NRR, -OC(S)NR-alkyl, -OC(S)NR-substituted alkyl, -OC(S)NR-alkenyl, -OC(S)NR-substituted alkenyl, -OC(S)NR-alkynyl, -OC(S)NR-substituted alkynyl, -OC(S)NR-cycloalkyl, -OC(S)NR-substituted cycloalkyl, 10 -OC(S)NR-aryl, -OC(S)NR-substituted aryl, -OC(S)NR-heteroaryl, -OC(S)NR-substituted heteroaryl, -OC(S)NR-heterocyclic, and -OC(S)NR-substituted heterocyclic where R is hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, 15 alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the groups -NRC(O)NRR, 20 -NRC(O)NR-alkyl, -NRC(O)NR-substituted alkyl, -NRC(O)NR-alkenyl, -NRC(O)NR-substituted alkenyl, -NRC(O)NR-alkynyl, -NRC(O)NR-substituted alkynyl, -NRC(O)NR-aryl, -NRC(O)NR-substituted aryl, -NRC(O)NR-cycloalkyl, -NRC(O)NR-substituted cycloalkyl, -NRC(O)NR-heteroaryl, and -NRC(O)NR-substituted heteroaryl, -NRC(O)NR-heterocyclic, and 25 -NRC(O)NR-substituted heterocyclic where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, 30 substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocabonylamino" refers to the groups -NRC(S)NRR, -NRC(S)NR-alkyl, -NRC(S)NR-substituted alkyl, -NRC(S)NR-alkenyl, -NRC(S)NR-substituted alkenyl, -NRC(S)NR-alkynyl, -NRC(S)NR-substituted alkynyl, -NRC(S)NR-aryl, -NRC(S)NR-substituted aryl, -NRC(S)NR-cycloalkyl, -NRC(S)NR-substituted cycloalkyl, -NRC(S)NR-heteroaryl, and -NRC(S)NR-substituted heteroaryl, -NRC(S)NR-heterocyclic, and -NRC(S)NR-substituted heterocyclic where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

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"Aryl" or "Ar" refers to a monovalent unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7yl, and the like). Preferred aryls include phenyl and naphthyl.

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"Substituted aryl" refers to aryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocabonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocabonyloxy, aminocabonylamino, aminothiocabonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic,

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5 carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted
 thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted
 thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl,
 substituted cycloalkyl, guanidino, guanidosulfone, halo, nitro, heteroaryl,
 10 substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy,
 substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy,
 heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino,
 oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl,
 -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl,
 15 -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted
 heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl,
 -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl,
 -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic,
 -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl,
 20 -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl,
 -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,
 -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl,
 -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted
 aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl,
 25 -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is
 hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted
 alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino,
 mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino,
 mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino,
 30 unsymmetric di-substituted amines having different substituents selected from the
 group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl,
 substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups
 on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz,
 formyl, and the like or substituted with -SO₂NRR where R is hydrogen or alkyl.

"Arylene" refers to a divalent unsaturated aromatic carbocyclic group of
 from 6 to 14 carbon atoms having a single ring (e.g., phenylene) or multiple

condensed rings (e.g., naphthylene or anthrylene) which condensed rings may or may not be aromatic. Preferred arylenes include phenylene and naphthylene. Substituted arylene refers to arylene groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino,

5 thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy,

10 heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted

15 thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy,

20 heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl, -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl,

25 -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,

30 -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl,

-NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO₂NRR where R is hydrogen or alkyl.

"Aryloxy" refers to the group aryl-O- which includes, by way of example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Aryloxyaryl" refers to the group -aryl-O-aryl.

"Substituted aryloxyaryl" refers to aryloxyaryl groups substituted with from 1 to 3 substituents on either or both aryl rings selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocabonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl,

thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted

5 heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl, -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl,

10 -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted

15 heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino,

20 mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and

25 substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO₂NRR where R is hydrogen or alkyl.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 carbon atoms

30 having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and the like. This definition also includes bridged groups such as bicyclo[2.2.1]heptane and bicyclo[3.3.1]nonane.

"Cycloalkyloxy" refers to -O-cycloalkyl.

"Cycloalkenyl" refers to cyclic alkenyl groups of from 3 to 10 carbon atoms
5 having a single cyclic ring.

"Cycloalkenyloxy" refers to -O-cycloalkenyl.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refers to an
10 cycloalkyl or cycloalkenyl group, preferably of from 3 to 10 carbon atoms, having
from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo
(=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy,
amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino,
aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy,
15 substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl,
cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl,
carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl,
carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl,
carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted
20 cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl,
thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl,
thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted
thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted
heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted
25 heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino,
oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl,
-OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl,
-OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is
hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl,
30 -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,
-NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl,

-NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkynyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

"Substituted cycloalkyloxy" and "substituted cycloalkenyloxy" refers to -O-substituted cycloalkyl and -O-substituted cycloalkenyloxy respectively.

"Cycloalkylene" refers to divalent cyclic alkylene groups of from 3 to 10 carbon atoms having a single cyclic ring including, by way of example, cyclopropylene, cyclobutylene, cyclopentylene, cyclooctylene and the like.

"Cycloalkenyloxy" refers to a divalent cyclic alkenylene groups of from 3 to 10 carbon atoms having a single cyclic ring.

"Substituted cycloalkylene" and "substituted cycloalkenyloxy" refers to a cycloalkylene or cycloalkenyloxy group, preferably of from 3 to 8 carbon atoms, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl,

aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl,
 substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl,
 halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted
 alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl,
 5 carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl,
 carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted
 cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl,
 thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl,
 thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted
 10 thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted
 heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted
 heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino,
 oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl,
 -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl,
 15 -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is
 hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl,
 -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,
 -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl,
 -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted
 20 aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl,
 -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is
 hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted
 alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino,
 mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino,
 25 mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino,
 unsymmetric di-substituted amines having different substituents selected from the
 group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl,
 substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted
 alkynyl groups having amino groups blocked by conventional blocking groups
 30 such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups
 substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted

alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

5 "Cycloalkoxy" refers to -O-cycloalkyl groups.

"Substituted cycloalkoxy" refers to -O-substituted cycloalkyl groups.

"Guanidino" refers to the groups -NRC(=NR)NRR, -NRC(=NR)NR-alkyl,
 10 -NRC(=NR)NR-substituted alkyl, -NRC(=NR)NR-alkenyl, -NRC(=NR)NR-substituted alkenyl, -NRC(=NR)NR-alkynyl, -NRC(=NR)NR-substituted alkynyl, -NRC(=NR)NR-aryl, -NRC(=NR)NR-substituted aryl, -NRC(=NR)NR-cycloalkyl, -NRC(=NR)NR-heteroaryl, -NRC(=NR)NR-substituted heteroaryl, -NRC(=NR)NR-heterocyclic, and
 15 -NRC(=NR)NR-substituted heterocyclic where each R is independently hydrogen and alkyl as well as where one of the amino groups is blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted
 20 heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"*N,N*-Dimethylcarbamyl" refers to the group -OC(O)N(CH₃)₂.

"Guanidinosulfone" refers to the groups -NRC(=NR)NRSO₂-alkyl,
 25 -NRC(=NR)NRSO₂-substituted alkyl, -NRC(=NR)NRSO₂-alkenyl, -NRC(=NR)NRSO₂-substituted alkenyl, -NRC(=NR)NRSO₂-alkynyl, -NRC(=NR)NRSO₂-substituted alkynyl, -NRC(=NR)NRSO₂-aryl, -NRC(=NR)NRSO₂-substituted aryl, -NRC(=NR)NRSO₂-cycloalkyl, -NRC(=NR)NRSO₂-substituted cycloalkyl, -NRC(=NR)NRSO₂-heteroaryl, and
 30 -NRC(=NR)NRSO₂-substituted heteroaryl, -NRC(=NR)NRSO₂-heterocyclic, and -NRC(=NR)NRSO₂-substituted heterocyclic where each R is independently hydrogen and alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted

alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

5 "Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is either chloro or bromo.

 "Heteroaryl" refers to an aromatic carbocyclic group of from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of
 10 oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl, indolyl and furyl.

 "Substituted heteroaryl" refers to heteroaryl groups which are substituted
 15 with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy,
 20 substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted
 25 heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted
 30 heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl,

-S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl,
 -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted
 heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl,
 -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl,
 5 -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic,
 -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl,
 -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl,
 -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,
 -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl,
 10 -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted
 aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl,
 -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is
 hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted
 alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino,
 15 mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino,
 mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino,
 unsymmetric di-substituted amines having different substituents selected from the
 group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl,
 substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups
 20 on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz,
 formyl, and the like or substituted with -SO₂NRR where R is hydrogen or alkyl.

"Heteroarylene" refers to a divalent aromatic carbocyclic group of from 2
 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of
 25 oxygen, nitrogen and sulfur within the ring. Such heteroarylene groups can have a
 single ring (e.g., pyridylene or furylene) or multiple condensed rings (e.g.,
 indolizinylenes or benzothienylene). Preferred heteroarylenes include pyridylene,
 pyrrolylene, indolyene and furylene.

30 "Substituted heteroarylene" refers to heteroarylene groups which are
 substituted with from 1 to 3 substituents selected from the group consisting of
 hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl,

alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocabonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl, -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and

di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by
5 conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO₂NRR where R is hydrogen or alkyl.

"Heteroaryloxy" refers to the group -O-heteroaryl and "substituted heteroaryloxy" refers to the group -O-substituted heteroaryl.

10

"Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can
15 be aryl or heteroaryl.

"Substituted heterocyclic" refers to heterocycle groups which are substituted with from 1 to 3 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino,
20 thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl,
25 carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted
30 thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted

heteroaryloxy, -C(O)O-aryl, -C(O)O-substituted aryl, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkynyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

25

Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide,

30

1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidine, tetrahydrofuranyl, and the like.

5

"Heterocyclene" refers to a divalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl.

10

"Substituted heterocyclene" refers to heterocyclene groups which are substituted with from 1 to 3 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino,

15

thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocabonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, -C(O)O-aryl, -C(O)O-substituted aryl, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl,

30

-NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl,
 -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic,
 -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl,
 -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl,
 5 -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic,
 -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and
 di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino,
 mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and
 di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and
 10 di-substituted heterocyclic amino, unsymmetric di-substituted amines having
 different substituents selected from the group consisting of alkyl, substituted alkyl,
 aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and
 substituted heterocyclic and substituted alkynyl groups having amino groups
 blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like
 15 or alkynyl/substituted alkynyl groups substituted with -SO₂-alkyl,
 -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl,
 -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl,
 -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and
 -SO₂NRR where R is hydrogen or alkyl.

20

"Heterocyclyloxy" refers to the group -O-heterocyclic and "substituted
 heterocyclyloxy" refers to the group -O-substituted heterocyclic.

25

"Thiol" refers to the group -SH.

"Thioalkyl" refers to the groups -S-alkyl.

"Substituted thioalkyl" refers to the group -S-substituted alkyl.

30

"Thiocycloalkyl" refers to the groups -S-cycloalkyl.

"Substituted thiocycloalkyl" refers to the group -S-substituted cycloalkyl.

"Thioaryl" refers to the group -S-aryl and "substituted thioaryl" refers to the group -S-substituted aryl.

5 "Thioheteroaryl" refers to the group -S-heteroaryl and "substituted thioheteroaryl" refers to the group -S-substituted heteroaryl.

"Thioheterocyclic" refers to the group -S-heterocyclic and "substituted thioheterocyclic" refers to the group -S-substituted heterocyclic.

10

"Amino" refers to the $-NH_2$ group.

"Substituted amino" refers to the $-NR'R''$ group wherein R' and R'' are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic or where R' and R'' , together with the nitrogen atom pendent thereto, form a heterocyclic ring.

15

20 "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of Formula (I), which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic

25 functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

Utility

The compounds and methods described herein provide for the sustained release of the GABA analog or active metabolite thereof relative to dosing with the parent drug itself. For example, GABA analogs such as gabapentin are useful
 5 in treating epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal damage, inflammation and irritable bowel disease. See, for example, WO 99/31075 which is incorporated herein by reference in its entirety. All of the amino acid linked drugs described herein can also be used as
 10 intermediates in order to couple them to bile acids as disclosed previously, as in U.S. Provisional Application No. 60/297,472 (attorney docket number 003053-013). U.S. Provisional Application No. 60/249,804 (attorney docket number 003053-006) and U.S. Provisional Application No. 60/297,594 (attorney docket number 003053-008) show GABA analogs coupled to Bile Acids through amino
 15 acid linkages. U.S. Provisional Application No. 60/297,654 (attorney docket number 003053-012) shows L-Dopa analogs coupled to Bile Acids through amino acid linkages. All of these provisional applications are incorporated herein by reference in their entirety.

20 Preferred Embodiments

This invention facilitates sustained therapeutic or prophylactic systemic blood concentrations of GABA analogues which heretofore could not be achieved.

Accordingly, in one of its compound aspects, this invention is directed to a
 25 compound of formula (I):



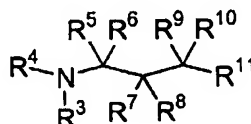
wherein

I is $-\text{NR}^{50}-(\text{CR}^{51}\text{R}^{52})_a-(\text{CR}^{53}\text{R}^{54})_b-\text{C}(\text{O})-$;
 30 J is $-\text{NR}^{55}-(\text{CR}^{56}\text{R}^{57})_c-(\text{CR}^{58}\text{R}^{59})_d-\text{C}(\text{O})-$;
 K is $-\text{NR}^{60}-(\text{CR}^{61}\text{R}^{62})_e-(\text{CR}^{63}\text{R}^{64})_f-\text{C}(\text{O})-$;

wherein a, b, c, d, e and f are independently 0 or 1, provided that at least one of a and b is 1, at least one of c and d is 1, and at least one of e and f is 1;

and wherein i, j and k are independently 0 or 1, provided that at least one of i, j and k is 1;

5 D is a moiety derived from a GABA analog having the following structure:



wherein

R³ is a covalent bond linking the GABA analog moiety to J_j;

10 R⁴ is hydrogen, or R⁴ and R⁹ together with the atoms to which they are attached form a heterocyclic ring;

R⁵ and R⁶ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

15 R⁷ and R⁸ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, or R⁷ and R⁸ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

20 R⁹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R¹⁰ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R¹¹ is C(O)R¹², wherein R¹² is a covalent bond linking the GABA analog moiety to K_k;

25 R⁵⁰ is hydrogen or R⁵⁰ and R⁵¹ together with the atoms to which they are attached form a heterocyclyl ring;

R⁵¹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl,

substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁵¹ and R⁵² together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R⁵¹ and R⁵³ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁵² is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁵³ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁵³ and R⁵⁴ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁵⁴ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁵⁵ is hydrogen or R⁵⁵ and R⁵⁶, together with the atoms to which they are attached form a heterocyclyl ring;

R⁵⁶ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁵⁶ and R⁵⁷ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R⁵⁶ and R⁵⁸ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁵⁷ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁵⁸ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or

R⁵⁸ and R⁵⁹ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁵⁹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R⁶⁰ is hydrogen or R⁶⁰ and R⁶¹, together with the atoms to which they are attached form a heterocyclyl ring;

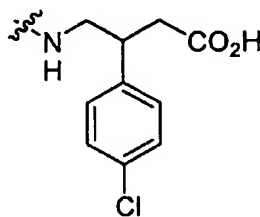
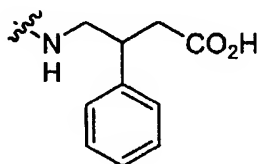
R⁶¹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁶¹ and R⁶² together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R⁶¹ and R⁶³ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁶² is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

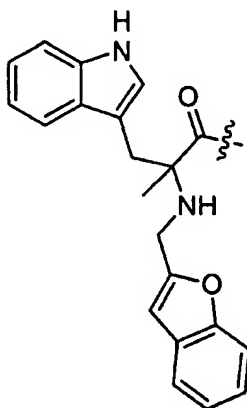
R⁶³ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R⁶³ and R⁶⁴ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R⁶⁴ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

and provided that when D is either of the following moieties



neither I or J are selected from a group of moieties selected from the following moieties: $\text{H}_2\text{NCH}_2\text{C(O)-}$, $\text{H}_2\text{NCH}(\text{CH}_3)\text{C(O)-}$, $\text{NH}_2\text{CH}_2\text{CH}_2\text{C(O)-}$ and

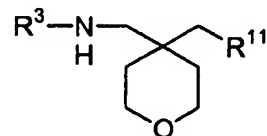
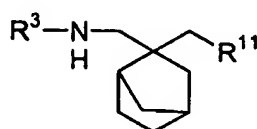
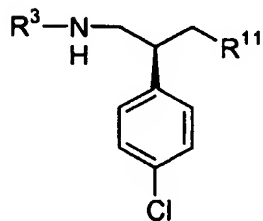
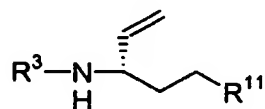
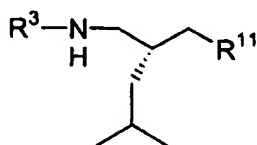
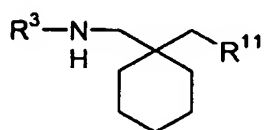


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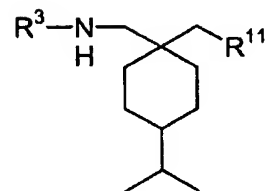
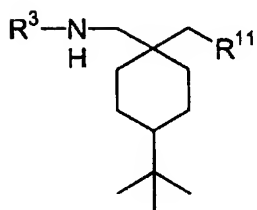
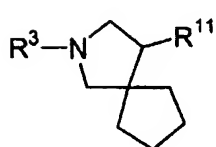
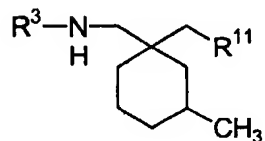
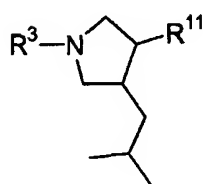
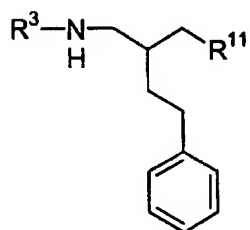
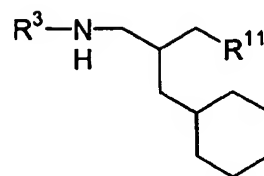
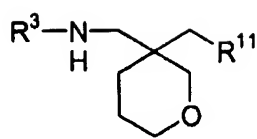
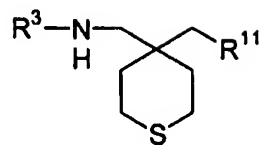
Preferably, in a compound of formula (I) k is 0 and j is 1.

Preferably, D in a compound of formula (I) is a moiety selected from a group consisting of the following GABA analog moieties:

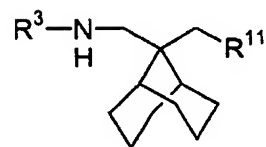
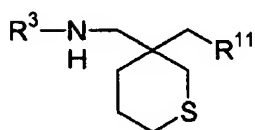
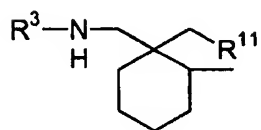
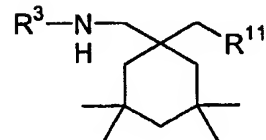
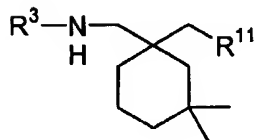
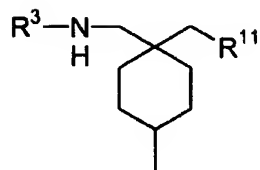
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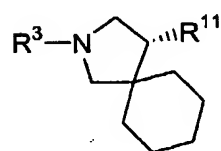
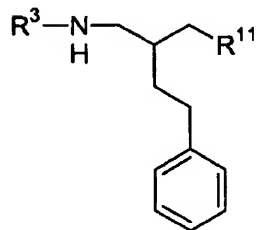
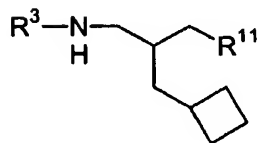
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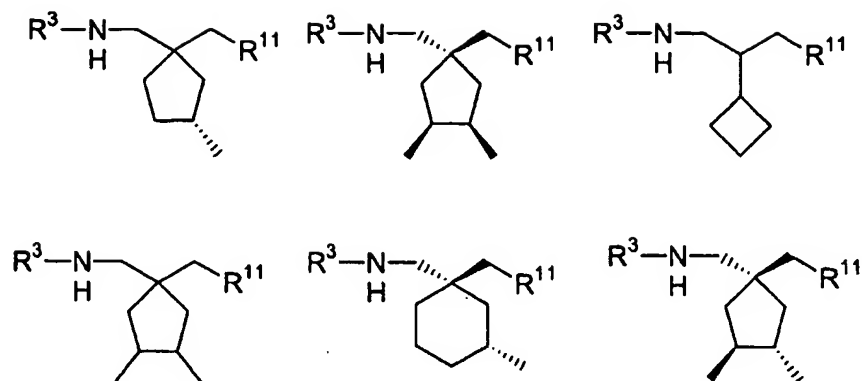


5



10





5

Preferably, in a compound of formula (I), a and c are 1 and b and d are 0.

Preferably, in a compound of formula (I), i and k are 0 and j is 1.

10

Preferably, in a compound of formula (I), I, J and K are derived from natural amino acids.

15

In a method aspect of this invention, the compounds of this invention are preferably used in a method for achieving sustained therapeutic or prophylactic blood concentrations of a GABA analog or an active metabolite thereof in the systemic circulation of an animal. The method involves administering a compound of formula (I) to an animal.

20

In a composition aspect of this invention, the compounds of this invention are mixed with a pharmaceutically acceptable carrier to provide a composition. The composition is preferably used in the method of achieving sustained therapeutic or prophylactic blood concentrations of a GABA analog or an active metabolite thereof discussed above.

25

Compound Preparation

Compounds of this invention can be made by various methods, including those illustrated in FIG. 1 and the working examples provided below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemie, or Sigma (St. Louis, Missouri, USA) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of formula (I) are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, subcutaneous, intravenous, intramuscular and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of formula (I) above associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted
5 by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions,
10 solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

15 In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to
20 provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth,
25 gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring
30 agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

5 The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 5000 mg, more usually about 10 to about 2000 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

10 The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual
15 compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation
20 composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid
25 preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 mg to about 2 g of the active ingredient of the present invention.

30 The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former.

The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl
5 alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous
10 solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and
15 suspensions in pharmaceutically acceptable, aqueous or organic solvents or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents
20 may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

25

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

30

EXAMPLES

In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

5	Atm	=	atmosphere
	Boc	=	<i>tert</i> -butyloxycarbonyl
	Cbz	=	carbobenzyloxy
	CPM	=	counts per minute
	DCC	=	dicyclohexylcarbodiimide
10	DMAP	=	4- <i>N,N</i> -dimethylaminopyridine
	DMEM	=	Dulbecco's minimum eagle medium
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethylsulfoxide
	Fmoc	=	9-fluorenylmethyloxycarbonyl
15	g	=	gram
	h	=	hour
	HBSS	=	Hank's buffered saline solution
	L	=	liter
	LC/MS	=	liquid chromatography/mass
20			spectroscopy
	M	=	molar
	min	=	minute
	mL	=	milliliter
	mmol	=	millimoles
25	NHS	=	N-hydroxysuccinimide
	PBS	=	phosphate buffered saline
	THF	=	tetrahydrofuran
	TFA	=	trifluoroacetic acid
	TMS	=	trimethylsilyl
30	μL	=	microliter
	μM	=	micromolar
	v/v	=	volume to volume

EXPERIMENTAL METHODS

5 EXAMPLE 1

Preparation of Aminoacyl-Gabapentin Derivatives - Method 1

To a 40 mL vial was added an N-Boc-protected amino acid (5 mmol), dicyclohexylcarbodiimide (1.24 g, 6 mmol), *N*-hydroxysuccinimide (0.7 g, 6 mmol), and acetonitrile (20 mL). The reaction mixture was shaken at 22-25°C for 4 h. The precipitated dicyclohexylurea was removed by filtration. To the filtrate was added an aqueous solution (30 mL) of Gabapentin hydrochloride (1.04 g, 6 mmol), and sodium hydroxide (0.4 g, 10 mmol). The reaction was stirred at 22-25°C for 16 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 0.5 M aqueous citric acid (2x100 mL) and water (2x100 mL). The organic phase was separated, dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was dissolved in trifluoroacetic acid (40 mL) and allowed to stand at 22-25°C for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in water (4 mL) and filtered through a 0.25 µm nylon membrane filter prior to purification by preparative HPLC (Phenomenex 250x21.2 mm, 5 µm LUNA C18 column, 100% water for 5 minutes, then 0-60% acetonitrile in water with 0.05% TFA over 20 minutes at 20 mL/min). The pure fractions were combined and the solvent was removed under reduced pressure to afford the product (1) (typically 70-90%) as a white solid.

25 L-Proline-Gabapentin (1a): MS (ESI) *m/z* 267.21 (M-H⁻), 269.28 (M+H⁺); ¹H NMR (DMSO-*d*₆): 1.2-1.6 (m, 10H, cyclohexyl), 1.8-2.4 (m, 6H), 3.0-3.4 (m, 4H), 4.2 (br s, 1H), 8.2 (t, 1H), 8.5 (br s, 1H), 9.4 (br s, 1H).

L-Isoleucine-Gabapentin (1b): MS (ESI) *m/z* 283.19 (M-H⁻), 285.18 (M+H⁺).

30 L-Asparagine-Gabapentin (1c): MS (ESI) *m/z* 284.19 (M-H⁻), 286.16 (M+H⁺).

L-Glutamine-Gabapentin (1d): MS (ESI) *m/z* 298.22 (M-H⁻), 300.19 (M+H⁺).

L-Leucine-Gabapentin (1e): MS (ESI) *m/z* 283.26 (M-H⁻), 285.25 (M+H⁺).

- L-Methionine-Gabapentin (1f): MS (ESI) m/z 301.10 (M-H⁻), 303.09 (M+H⁺).
L-Phenylglycine-Gabapentin (1g): MS (ESI) m/z 303.15 (M-H⁻), 305.13 (M+H⁺).
L-Serine-Gabapentin (1h): MS (ESI) m/z 257.11 (M-H⁻), 259.10 (M+H⁺).
L-Phenylalanine-Gabapentin (1i): MS (ESI) m/z 317.20 (M-H⁻), 319.20 (M+H⁺).
5 L-Threonine-Gabapentin (1j): MS (ESI) m/z 271.35 (M-H⁻), 273.33 (M+H⁺).
L-Aspartyl-Gabapentin (1k): MS (ESI) m/z 285.35 (M-H⁻), 287.33 (M+H⁺).
L-Glutamyl-Gabapentin (1l): MS (ESI) m/z 299.08 (M-H⁻), 301.05 (M+H⁺).
L-Tyrosine-Gabapentin (1m): MS (ESI) m/z 333.14 (M-H⁻), 335.14 (M+H⁺).
L-Histidine-Gabapentin (1n): MS (ESI) m/z 307.16 (M-H⁻), 309.14 (M+H⁺).
10 L-Lysine-Gabapentin (1o): MS (ESI) m/z 298.22 (M-H⁻), 300.19 (M+H⁺).
 β -Alanine-Gabapentin (1p): MS (ESI) m/z 241.23 (M-H⁻), 243.26 (M+H⁺).
 α -Aminoisobutyryl-Gabapentin (1q): MS (ESI) m/z 255.26 (M-H⁻), 257.28 (M+H⁺).
D-Alanine-Gabapentin (1r): MS (ESI) m/z 241.24 (M-H⁻), 243.27 (M+H⁺).
15 Glycine-Gabapentin (1s): MS (ESI) m/z 227.29 (M-H⁻), 229.24 (M+H⁺).

Preparation of Aminoacyl-Gabapentin Derivatives - Method 2

- To an ice-cold reaction mixture containing an N-Boc-protected amino acid (1 mmol) and triethylamine (0.278 mL, 2 mmol) in anhydrous THF (100 mL) was
20 added ethyl chloroformate (0.115 mL, 1.2 mmol). The reaction mixture was stirred at 0°C for 30 min. A solution of Gabapentin hydrochloride salt (311 mg, 1.5 mmol) in 0.5 N NaOH (6 mL) was added at 0°C, stirred for 30 min at 0°C and then 30 min at room temperature. After evaporation of the THF under reduced pressure, saturated citric acid (20 mL) was added. The product was extracted with
25 ethyl acetate (3x30 mL) and the combined organic phase dried over MgSO₄ and concentrated to dryness. The resulting residue was treated with 80% (v/v) TFA in dichloromethane at room temperature for 30 min. The reaction mixture was evaporated to dryness. The aminoacyl-Gabapentin product was purified by preparative HPLC as described above.

30

L-Asparagine-Gabapentin (1c): MS (ESI) m/z 286.5 ($M+H^+$); 1H NMR (CD_3OD): 1.27-1.62 (m, 10H cyclohexyl), 2.36 (s, 2H, CH_2), 2.72-2.82 (m, 2H, CH_2), 3.28 (d, 1H, CH_2), 3.55 (d, 1H, CH_2), 4.21 (m, 1H, CH).

- 5 L-Leucine-Gabapentin (1e): MS (ESI) m/z 285.5 ($M+H^+$); 1H NMR (CD_3OD): 1.06 (m, 6H, $2 \times CH_3$), 1.33-1.60 (m, 10H cyclohexyl), 1.72 (m, 3H, CH and CH_2), 2.32 (s, 2H, CH_2), 3.32 (d, 1H, CH_2), 3.50 (d, 1H, CH_2), 3.95 (m, 1H, CH).

EXAMPLE 2

10 *In Vitro Compound Transport Assays with PEPT1 and PEPT2-Expressing Cell Lines*

(a) Inhibition of Radiolabeled Gly-Sar Uptake

- Rat and human PEPT1 and PEPT2 expressing CHO cell lines were prepared as described in PCT Application WO01/20331. Gabapentin-containing dipeptides
15 were evaluated for interaction with the peptide transporters using a radiolabeled substrate uptake assay in a competitive inhibition format, as described in PCT Application WO01/20331. Transport-induced currents were also measured in *Xenopus* oocytes transfected with rat and human PEPT1 and PEPT2.

20 (b) Analysis of Electrogenic Transport in *Xenopus* Oocytes

- RNA preparation: Rat and human PEPT1 and PEPT2 transporter cDNAs were subcloned into a modified pGEM plasmid that contains 5' and 3' untranslated sequences from the *Xenopus* β -actin gene. These sequences increase RNA stability and protein expression. Plasmid cDNA was linearized and used as
25 template for *in vitro* transcription (Epicentre Technologies transcription kit, 4:1 methylated:non-methylated GTP).

- Xenopus* oocyte isolation. *Xenopus laevis* frogs were anesthetized by immersion in Tricaine (1.5 g/mL in deionized water) for 15 min. Oocytes were removed and
30 digested in frog ringer solution (90 mM NaCl, 2 mM KCl, 1 mM $MgCl_2$, 10 mM NaHEPES, pH 7.45, no $CaCl_2$) with 1 mg/mL collagenase (Worthington Type 3) for 80-100 min with shaking. The oocytes were washed 6 times, and the buffer

changed to frog ringer solution containing CaCl_2 (1.8 mM). Remaining follicle cells were removed if necessary. Cells were incubated at 16° C, and each oocyte injected with 10-20 μg RNA in 45 μL solution.

- 5 Electrophysiology measurements. Transport currents were measured 2-14 days after injection, using a standard two-electrode electrophysiology set-up (Geneclamp 500 amplifier, Digidata 1320/PCLAMP software and ADInstruments hardware and software were used for signal acquisition). Electrodes (2-4 $\text{m}\Omega$) were microfabricated using a Sutter Instrument puller and filled with 3M KCl.
- 10 The bath was directly grounded (transporter currents were less than 0.3 μA). Bath flow was controlled by an automated perfusion system (ALA Scientific Instruments, solenoid valves).

- For transporter pharmacology, oocytes were clamped at -60 to -90 mV, and
- 15 continuous current measurements acquired using PowerLab Software and an ADInstruments digitizer. Current signals were lowpass filtered at 20 Hz and acquired at 4-8 Hz. All bath and drug-containing solutions were frog ringers solution containing CaCl_2 . Drugs were applied for 10-30 seconds until the induced current reached a new steady-state level, followed by a control solution
- 20 until baseline currents returned to levels that preceded drug application. The difference current (baseline subtracted from peak current during drug application) reflected the net movement of charge resulting from electrogenic transport and was directly proportional to transport rate. Recordings were made from a single oocyte for up to 60 min, enabling 30-40 separate compounds to be tested per
- 25 oocyte. Compound-induced currents were saturable and gave half-maximal values at substrate concentrations comparable to radiolabel competition experiments. To compare results between oocytes expressing different levels of transport activity, a saturating concentration of glycyl-sarcosine (1 mM) was used as a common reference to normalize results from test compounds. Using this
- 30 normalization procedure V_{max} (i.e. maximal induced current) for different compounds tested on different oocytes could be compared.

Table 1: *In vitro* transport data for selected compounds on rPEPT1-expressing cells

COMPOUND	IC ₅₀ (μ M)	% Max. (Gly-Sar)
(1i)	56	52

IC₅₀ data from radiolabeled competition assay in transporter-expressing CHO cells
%Max response (relative to Gly-Sar) from transporter-expressing oocytes at a test compound concentration of 1 mM

Table 2: *In vitro* transport data for selected compounds on rPEPT2-expressing cells

COMPOUND	IC ₅₀ (μ M)	% Max. (Gly-Sar)
(1i)	ND	77

IC₅₀ data from radiolabeled competition assay in transporter-expressing CHO cells
%Max response (relative to Gly-Sar) from transporter-expressing oocytes at a test compound concentration of 1 mM

EXAMPLE 3

In Vitro Enzymatic Release of Gabapentin from Aminoacyl-Gabapentin Conjugates

Tissues were obtained from commercial sources (e.g., Pel-Freez Biologicals, Rogers, AR, or GenTest Corporation, Woburn, MA). Stability of prodrugs towards specific enzymes (e.g., carboxypeptidase A, aminopeptidase) was also evaluated by incubation with the purified enzyme. Experimental conditions used for the *in vitro* studies are described in Table 3 below. Each preparation was incubated with test compound at 37°C for one hour. Aliquots (50 μ L) were removed at 0, 30, and 60 min and quenched with 0.1% trifluoroacetic acid in acetonitrile. Samples were then centrifuged and analyzed for the presence of prodrug and released Gabapentin by LC/MS/MS as described below.

The stability of Gabapentin-containing prodrugs to Caco-2 homogenates was evaluated as follows:

5 *Caco-2 Homogenate S9 Stability:* Caco-2 cells were grown for 21 days prior to harvesting. Culture medium was removed and cell monolayers were rinsed and scraped off into ice-cold 10 mM sodium phosphate/0.15 M potassium chloride, pH 7.4. Cells were lysed by sonication at 4°C using a probe sonicator. Lysed cells were then transferred into 1.5 mL centrifuge vials and centrifuged at 9000 g for 20 min at 4°C. The resulting supernatant (Caco-2 cell homogenate S9
10 fraction) was aliquoted into 0.5 mL vials and stored at -80°C until used. For stability studies, prodrug (5 µM) was incubated in Caco-2 homogenate S9 fraction (0.5 mg protein per mL) for 60 min at 37°C. Concentrations of intact prodrug and released drug were determined at zero time and 60 minutes using LC/MS/MS.

15 *Aminopeptidase Stability:* Aminopeptidase 1 (Sigma catalog # A-9934) was diluted in deionised water to a concentration of 856 units/mL. Stability studies were conducted by incubating prodrug (5 µM) with 0.856 units/mL aminopeptidase 1 in 50 mM Tris-HCl buffer at pH 8.0 and 37°C. Concentrations
20 of intact prodrug and released drug were determined at zero time and 60 minutes using LC/MS/MS.

Concentrations of prodrug or Gabapentin in tissue extracts were determined by direct injection onto an API 2000 LC/MS/MS equipped with an Agilent 1100
25 binary pump and autosampler. Separation was achieved using a 3.5 µm Zorbax Ellipse XDB-C8 4.4 x 150 mm column heated to 45°C during the analysis. The mobile phases were: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B). The gradient condition was: 2% B for 0.5 min, increasing to 90% B in 2.0 min, maintained for 2.5 min and returning to 2% B for 2 min. A
30 TurboIonSpray source was used on the API 2000. The analysis was performed in the positive ion mode and MRM transitions of 172.0/137.2 were used in the

analysis of Gabapentin (2). Ten microliters of the sample extracts were injected. Peaks were integrated using Analyst quantitation software. The method was linear for (2) over the concentration range 0.002 to 2.5 µg/mL respectively.

- 5 Representative *in vitro* metabolism data are reported below for Gabapentin prodrugs (1i), (1k) and (1p) in Table 3 below:

Table 3. *In Vitro* Enzymatic Release of Gabapentin (2) in 60 minutes from Representative Aminoacyl-Gabapentin Prodrugs

10

Preparation	Substrate Concentration	Cofactors	% (2) from (1i)	% (2) from (1k)	% (2) from (1p)
Rat Plasma	2.0 µM	None	19	NR	NR
Human Plasma	2.0 µM	None	NR	NR	NR
Rat Liver S9 (0.5 mg/mL)	2.0 µM	NADPH	1	NR	NR
Human Liver S9 (0.5 mg/mL)	2.0 µM	NADPH	1	NR	NR
Human Intestine S9 (0.5 mg/mL)	2.0 µM	NADPH	5	NR	NR
Rat Intestinal Wash	5.0 µM	None	ND	ND	ND
Caco-2 Homogenate	5.0 µM	None	21	6	NR
Amino-peptidase	5.0 µM	None	24	NR	NR

ND = Not determined. NR = Not released

- 15 In view of the above disclosure, it is understood, of course, that combinations of substituents within the compounds of the present invention do not include any combination that is chemically impossible or non-feasible as would be appreciated by one skilled in the art.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



wherein

I is $-\text{NR}^{50}-(\text{CR}^{51}\text{R}^{52})_a-(\text{CR}^{53}\text{R}^{54})_b-\text{C}(\text{O})-$;

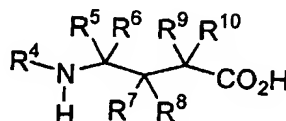
J is $-\text{NR}^{55}-(\text{CR}^{56}\text{R}^{57})_c-(\text{CR}^{58}\text{R}^{59})_d-\text{C}(\text{O})-$;

10 K is $-\text{NR}^{60}-(\text{CR}^{61}\text{R}^{62})_e-(\text{CR}^{63}\text{R}^{64})_f-\text{C}(\text{O})-$;

wherein a, b, c, d, e and f are independently 0 or 1, provided that at least one of a and b is 1, at least one of c and d is 1, and at least one of e and f is 1;

and wherein i, j and k are independently 0 or 1, provided that at least one of i, j and k is 1;

15 D is a moiety derived from a GABA analog having of the following structure:



wherein

20 R^3 is a covalent bond linking the GABA analog moiety to J_j ;

R^4 is hydrogen, or R^4 and R^9 together with the atoms to which they are attached form a heterocyclic ring;

25 R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, or R^7 and R^8 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

30

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{11} is $C(O)R^{12}$, wherein R^{12} is a covalent bond linking the GABA analog moiety to K_k ;

R^{50} is hydrogen or R^{50} and R^{51} together with the atoms to which they are attached form a heterocyclyl ring;

R^{51} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{51} and R^{52} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R^{51} and R^{53} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R^{52} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R^{53} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R^{53} and R^{54} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R^{54} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R^{55} is hydrogen or R^{55} and R^{56} , together with the atoms to which they are attached form a heterocyclyl ring;

R^{56} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or

R⁵⁶ and R⁵⁷ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R⁵⁶ and R⁵⁸ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

5 R⁵⁷ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

 R⁵⁸ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or
10 R⁵⁸ and R⁵⁹ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

 R⁵⁹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;
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 R⁶⁰ is hydrogen or R⁶⁰ and R⁶¹, together with the atoms to which they are attached form a heterocyclyl ring;

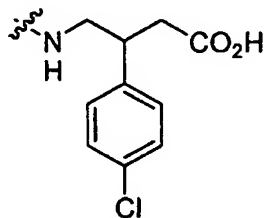
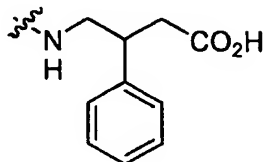
 R⁶¹ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or
20 R⁶¹ and R⁶² together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring, or R⁶¹ and R⁶³ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

25 R⁶² is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

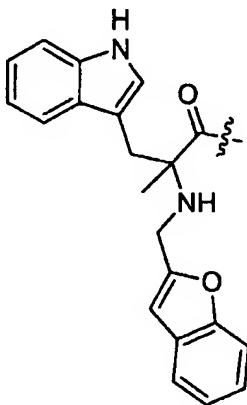
 R⁶³ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or
30 R⁶³ and R⁶⁴ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclyl or substituted heterocyclyl ring;

R^{64} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

- 5 and provided that when D is either of the following moieties



neither I or J are selected from a group of moieties selected from the following moieties: H₂NCH₂C(O)-, H₂NCH(CH₃)C(O)-, NH₂CH₂CH₂C(O)- and



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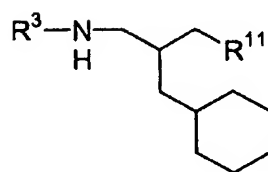
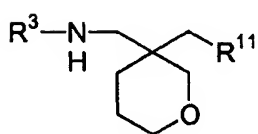
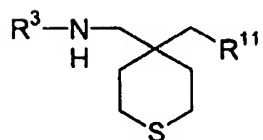
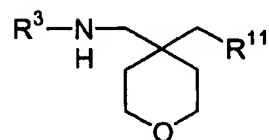
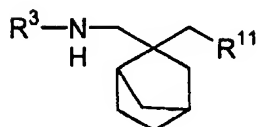
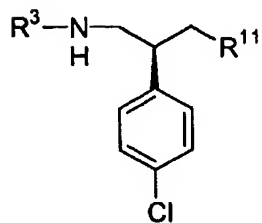
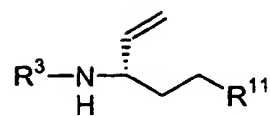
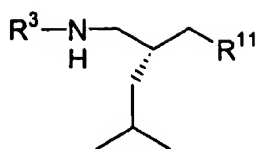
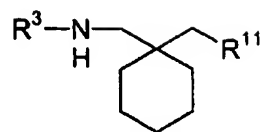
2. The compound according to Claim 1, wherein k is 0.

3. The compound according to Claim 2, wherein i is 0.

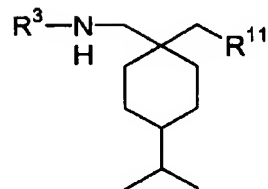
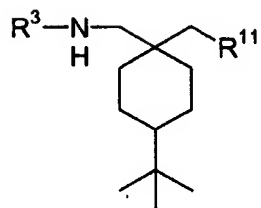
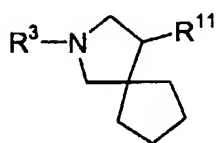
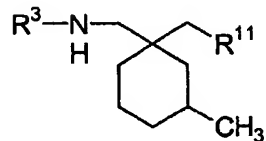
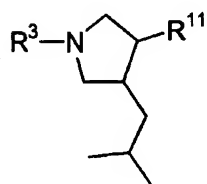
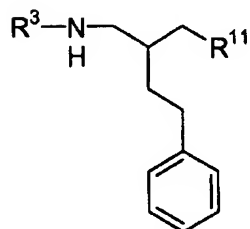
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4. The compound according to Claim 2, wherein j is 1.

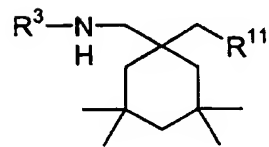
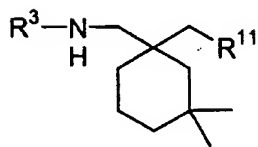
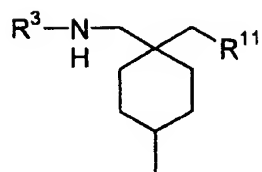
5. The compound according to Claim 4, wherein D is selected from a group consisting of the following GABA analog moieties:

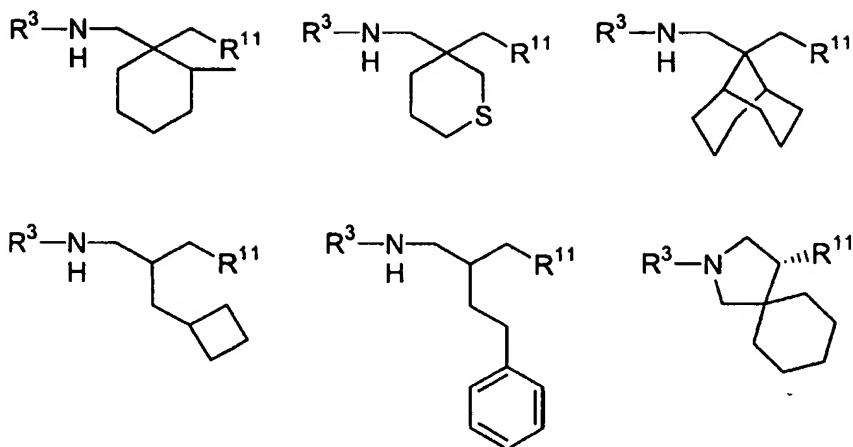


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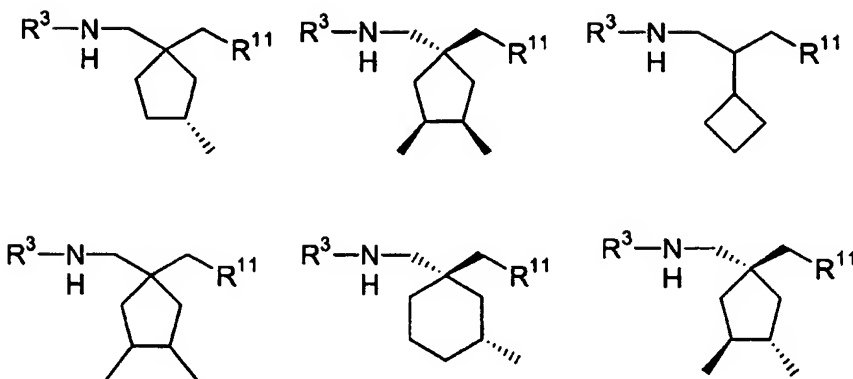


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6. The compound according to Claim 5, wherein a and c are 1, and wherein b and d are 0.

7. The compound according to Claim 6, wherein i is 0.

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8. The compound according to Claim 7, wherein J is derived from a natural amino acid.

Synthesis of Aminoacyl and Other Peptide Derivatives of GABA Analogs

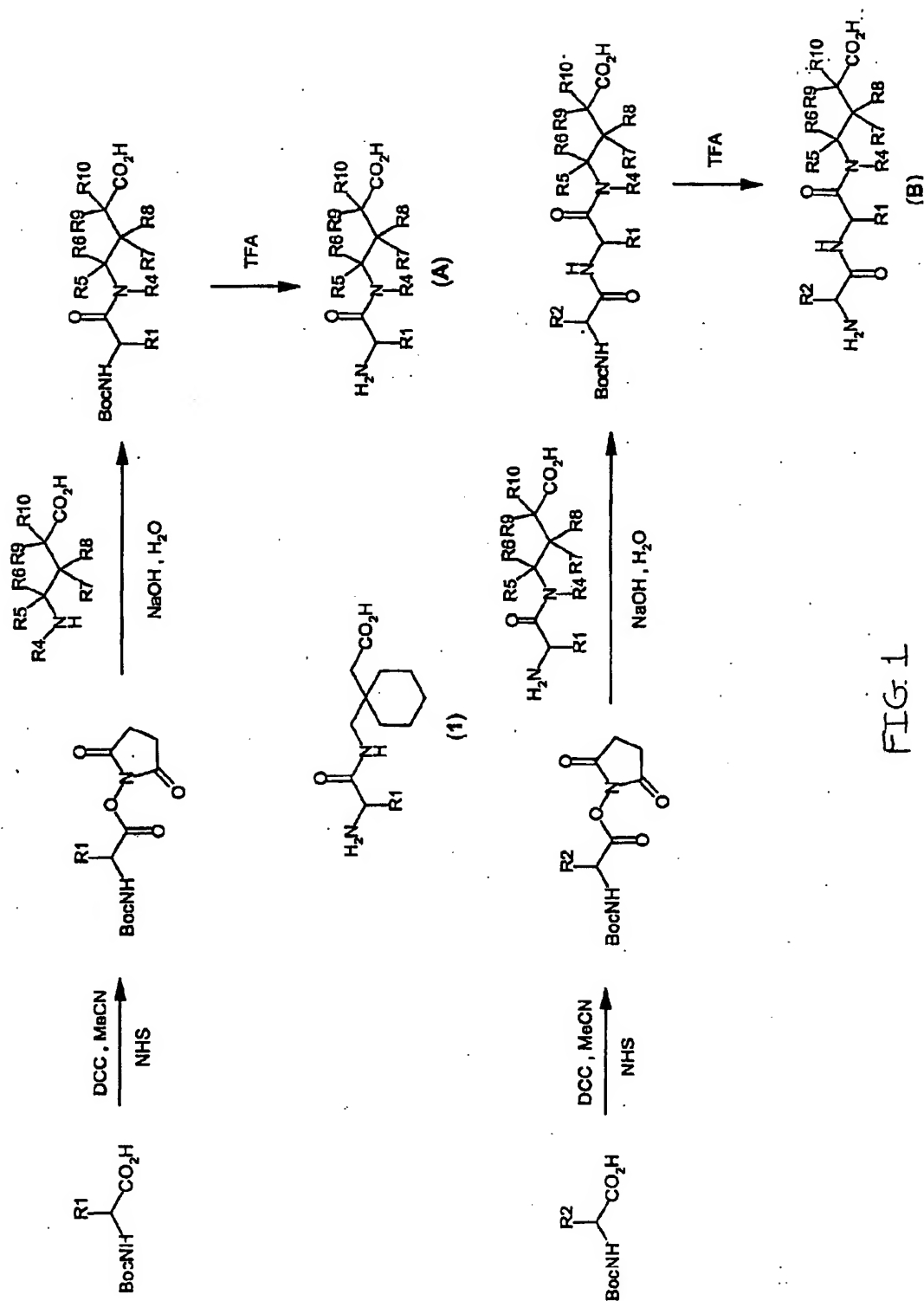


FIG. 1